Explore the Rationale for the Dual Mechanism CCB/ARB Approach in Hypertension Management

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Global Mortality 2000: Impact of Hypertension and Other Health Risk Factors

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Attributable mortality in millions (total: 55,861,000)

- High BP
- Tobacco
- High cholesterol
- Underweight
- Unsafe sex
- High BMI
- Physical inactivity
- Alcohol

Developing region
Developed region

Attributable mortality in millions (total: 55,861,000)
Stroke and Ischemic Heart Disease (IHD) Mortality Rate in Each Decade of Age, Versus Usual Systolic BP at the Start of that Decade

<table>
<thead>
<tr>
<th>Age</th>
<th>Stroke Age at Risk</th>
<th>Stroke Usual SBP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50–59 y</td>
<td>256</td>
<td>0</td>
</tr>
<tr>
<td>60–69 y</td>
<td>128</td>
<td>2 mmHg decrease in mean SBP</td>
</tr>
<tr>
<td>70–79 y</td>
<td>64</td>
<td>7% ischaemic heart disease mortality</td>
</tr>
<tr>
<td>80–89 y</td>
<td>32</td>
<td>10% stroke mortality</td>
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<th>Age</th>
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*Floating absolute risk and 95% CI

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Half of Hypertensive Patients still not at goal

Patients (%)

<table>
<thead>
<tr>
<th>Country</th>
<th>BP goal achieved</th>
<th>BP goal not achieved</th>
</tr>
</thead>
<tbody>
<tr>
<td>England</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Sweden</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>Spain</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>Italy</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>Korea</td>
<td></td>
<td>46</td>
</tr>
</tbody>
</table>

*Treated for hypertension
BP goal is <140/90 mmHg

Multiple Antihypertensive Drugs Required to Achieve Target BP

**UKPDS, ABCD, MDRD, HOT, AASK, IDNT, ASCOT=average; ALLHAT=mean.**

>60-70% patients need 2 or more anti-hypertensive agents in Korea Practice.

- 2 drug combination Rx takes the largest portion across all the specialties.

<table>
<thead>
<tr>
<th>Specialty</th>
<th>Mono Tx</th>
<th>2 drug combi</th>
<th>3 drug combi</th>
<th>4+ drug combi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardio (n=50)</td>
<td>26</td>
<td>40</td>
<td>23</td>
<td>11</td>
</tr>
<tr>
<td>Endo (n=30)</td>
<td>35</td>
<td>41</td>
<td>18</td>
<td>6</td>
</tr>
<tr>
<td>Nephro (n=30)</td>
<td>28</td>
<td>36</td>
<td>24</td>
<td>12</td>
</tr>
<tr>
<td>Clinic (n=60)</td>
<td>38</td>
<td>40</td>
<td>18</td>
<td>4</td>
</tr>
</tbody>
</table>

(Unit: mean %)

[Base: HTN patients on medication]

* FDC is considered as 2 drug combination.

* 2007 CV portfolio optimization study
Blood Pressure has Multiple Regulatory Pathways

Patient 1

Patient 2

Patient 3

- Sympathetic nervous system
- Renin-angiotensin system
- Total body sodium

B. Waeber, March 2007, with permission
Contemporary Hypertension and its Therapeutic Strategy

- Understand burden of Hypertension
  - Poor Treatment and control rates

- Rationale for Multiple-mechanism Therapy in Hypertension
  - Inadequacy of agents with a single mechanism of action

Inadequacy of Single MOA approach

Advantages of Multiple-mechanism Therapy
**ESH–ESC Recommendations for 6 Combining BP-lowering Drugs and Availability as Fixed-dose Combinations**

Diuretics

- **β-blockers**
- **α-blockers**
- Angiotensin-converting enzyme (ACE) inhibitors
- Angiotensin receptor blockers (ARBs)
- Calcium channel blockers (CCBs)

Available as a fixed-dose combination

Less frequently used/combination used as necessary

Adapted from Task Force of ESH–ESC. J Hypertens 2007;25:1105–87
A Notable Absentee From Currently Available Dual-Mechanism Agents is the CCB–ARB

- Angiotensin-converting enzyme (ACE) inhibitor and CCB
  - Benazepril + amlodipine (Lotrel)
  - Trandolapril + verapamil (Tarka)
  - Ramipril + felodipine (Unimax)
- ACE inhibitor and diuretic
  - Benazepril + HCTZ (Lotensin HCTZ)
  - Captopril + HCTZ (Capoten)
- ARB and diuretic
  - Valsartan + HCTZ (Diovan HCTZ/Co-Diovan)
  - Losartan + HCTZ (Hyzaar HCTZ)
- β-blocker and diuretic
  - Atenolol + chlorthalidone (Tenoretic)
  - Metoprolol + HCTZ (Lopressor HCT)
- β-blocker and CCB
  - Metoprolol + felodipine (Logimax)
  - Atenolol + nifedipine (Nif-Ten)
- CCB and diuretic
  - Nifedipine + mefruside (Sali-Adalat)

Notable absentee is a CCB + ARB
Interaction of CCBs and ARBs on Vascular and Renal Function, SNS and RAS Activity
Amlodipine/Valsartan:
BP Lowering Across All Grades of Hypertension

Mean change in MSSBP from baseline (mmHg)

<table>
<thead>
<tr>
<th>Grade 1 HTN</th>
<th>Grade 2 HTN</th>
<th>Grade 2–3 HTN</th>
<th>Grade 3 Systolic BP ≥180 mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=69</td>
<td>n=140</td>
<td>n=64</td>
<td>n=15</td>
</tr>
<tr>
<td>-20</td>
<td>-30</td>
<td>-36</td>
<td>-43</td>
</tr>
</tbody>
</table>

DBP reduction (mmHg)  -17  -18  -29  -26

Data from Poldermans et al. Clin Ther 2007;29:279–89. Dose 5–10/160 mg
Reduced Fluid Retention with Amlodipine/Valsartan Compared with Amlodipine Monotherapy

- Amlodipine 10mg: 23.0
- Amlodipine/Valsartan 10/160 mg: 6.8

70% difference

*p<0.01 vs. amlodipine, n=80

Complementary Effects of a CCB/RAS Inhibitor: Reduction of CCB-associated Edema

Arterial hypertension
- Constricted blood vessels, high resistance

CCBs
- BP reduction due to arterial vasodilation
- Tendency towards edema due to absent venodilation
- BP reduction stimulates RAS and increases angiotensin II level

CCBs + RAS inhibitors*
- Blockade of RAS inhibits effects of angiotensin II, giving rise to additional BP reduction
- Additional venodilation by RAS inhibitors reduces edema

*Angiotensin receptor blockers or angiotensin-converting enzyme inhibitors

CCB/ARB: Synergy of Counter-regulation

CCB
- Arteriodilation
- Peripheral edema
- Effective in low-renin patients
- Proven efficacy in elderly

ARB
- RAS blockade
- CHF and renal benefits
- DM benefits

ARB
- Arterio-Venodilation
- Attenuates peripheral edema
- Effective in high-renin patients
- Better in younger

CCB
- RAS activation
- No renal or CHF benefits
- No DM benefits
Avoiding Cardiovascular Events through COMbination Therapy in Patients Living with Systolic Hypertension

A prospective, double-blind, randomized, trial
to compare the effects of
amlodipine / benazepril vs. benazepril / thiazide
on the reduction of CV morbidity and mortality
in patients with high risk hypertension
ACCOMPLISH: Design

Titrated to achieve BP <140/90 mmHg; <130/80 mmHg in patients with diabetes or renal insufficiency.

Screening

Randomization

- Amlodipine 5 mg/benazepril 20 mg
- Benazepril 20 mg + HCTZ 12.5 mg
- Benazepril 40 mg + HCTZ 12.5 mg
- Benazepril 40 mg + HCTZ 25 mg

Month 1

- Amlodipine 5 mg/benazepril 40 mg
- Benazepril 40 mg + HCTZ 12.5 mg

Month 2

- Amlodipine 10 mg/benazepril 40 mg

Month 3

- Free add-on antihypertensive agents*

Year 5

*Beta blockers; alpha blockers; clonidine; loop diuretics.

Systolic Blood Pressure over Time

![Graph showing systolic blood pressure reduction over time with ACEI/HCTZ and CCB/ACEI treatments.](image)

- **ACEI / HCTZ**
  - N=5733
- **CCB / ACEI**
  - N=5713

**Difference of 0.7 mmHg p<0.05**

- **130 mmHg**
- **129.3 mmHg**

2008 ACC
ACCOMPLISH: Exceptional Control Rates with Initial Combination Therapy

Control rate (%)

ACEI / HCTZ
N=5733

CCB / ACEI
N=5713

Baseline Control Rates

78.5
37.2

81.7
37.9

P<0.001 at 30 months follow-up
Control defined as <140/90 mmHg

2008 ACC
Kaplan Meier for Primary Endpoint

Cumulative event rate

HR (95% CI): 0.80 (0.72, 0.90)

Time to 1st CV morbidity/mortality (days)

INTERIM RESULTS Mar 08

CCB / ACEI

ACEI / HCTZ

20% Risk Reduction

P=0.002

2008 ACC
Primary and Other Endpoints

Incidence of adjudicated primary endpoints, based upon cut-off analysis date 3/24/2008

(Intent-to-treat population)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Risk Ratio (95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite CV mortality/morbidity</td>
<td>0.80 (0.72–0.90)</td>
</tr>
<tr>
<td>Primary w/o revascularization</td>
<td>0.79 (0.68–0.92)</td>
</tr>
<tr>
<td>Hard CV endpoint (CV death, non-fatal MI, non-fatal stroke)</td>
<td>0.80 (0.68–0.94)</td>
</tr>
<tr>
<td>All cause mortality</td>
<td>0.90 (0.75–1.08)</td>
</tr>
</tbody>
</table>

Risk Ratio

0.5 1.0 2.0
Favors CCB / ACEI Favors ACEI / HCTZ

2008 ACC
EXPRESS-C Study Design
Non-responders to Combination Therapy (Ramipril/Felodipine)

- 133 patients in 16 centers
- Open, sequential, non-responder study including patients with moderate hypertension (160 mmHg < SBP < 180 mmHg)
- Initial treatment: ramipril 5 mg + felodipine 5 mg (highest permitted dosage in fixed-dose combination)
- **Uncontrolled patients** (n=105) (SBP >140 mmHg) were treated with Amlodipine/Valsartan 10/160 mg for another 5 weeks

Trenkwalder et al. DMW 2006;131:S164
Additional Reduction in BP with Amlodipine/Valsartan in Non-responders to Ramipril/Felodipine

Open, sequential, non-responder, 10-week study

N=133

Mean systolic BP (mmHg)

Week 0 5 10

After Ram 5 + Fel 5

After Amlo/Val 10/160

166.7

151.4

136

Mean diastolic BP (mmHg)

Week 0 5 10

After Ram 5 + Fel 5

After Amlo/Val 10/160

96.6

89.3

82.3

-30.7 mmHg

-15.4 mmHg

p<0.0001

-14.3 mmHg

-7.0 mmHg

p<0.0001

Trenkwalder et al. DMW 2006;131:S164
VALUE Suggests Immediate BP Control Reduce Cardiac M&M

Pooled Treatment Groups

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Immediate responders (n = 9336)</th>
<th>Non-immediate responders (n = 5663)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatal/ Non-fatal cardiac events</td>
<td>0.88 (0.79–0.97)</td>
<td>0.83 (0.71–0.98)</td>
</tr>
<tr>
<td>Fatal/ Non-fatal stroke</td>
<td>0.90 (0.81–0.99)</td>
<td></td>
</tr>
<tr>
<td>All-cause death</td>
<td>0.89 (0.76–1.04)</td>
<td>0.87 (0.75–1.01)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure hospitalizations</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Those not on previous treatment: SBP ↓ ≥10 mmHg at one month; those on previous treatment: SBP ≤ baseline at one month.

**P < 0.05; †P < 0.01.


Park JB 2008 Apr
Many Advantages of Combinations “ARB + CCB” Over Monotherapy for Hypertension

- **Efficacy**
  - Faster achievement of target BP
  - Higher control rates

- **Safety**
  - Potential for fewer side effects

- **Compliance**
  - Improved compliance by simple, convenient regimen

Increased potential for end-organ protection

Improved CV outcomes